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**Proximal and Distal Intestinal Calcium Transport in vitro
as Influenced by Low Calcium Diet, Uremia,
Parathyroidectomy and 1,25-Dihydroxycholecalciferol
Treatment in Rats**

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Proximal and Distal Intestinal Calcium Transport *in vitro* as Influenced by Low Calcium Diet, Uremia, Parathyroidectomy and 1,25-Dihydroxycholecalciferol Treatment in Rats

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Summary. Duodenal and ileal *in vitro* calcium transport was studied in 5/6 nephrectomized rats. Low calcium diet resulted in an increase of the duodenal calcium transport in kidney intact control animals but not in uremic rats; the ileal transport however increased in controls as well as in uremic rats. Parathyroidectomy decreased this adaptive transport at both gut sites in intact and uremic rats. Supplementation with low doses of 1,25-dihydroxycholecalciferol (1,25-DHCC) restored the duodenal transport in nephrectomized rats to the level of controls; nephrectomized plus parathyroidectomized animals increased the duodenal but not the ileal calcium transport. A close correlation between calcium transport and serum phosphorus concentrations of all groups of rats studied points towards a possible role of phosphate for intestinal calcium transport. It is concluded that duodenal calcium transport is regulated by the parathyroid-1,25-DHCC axis with 1,25-DHCC as effector; ileal calcium transport in contrast is regulated by combined direct effects of 1,25-DHCC and parathyroid hormone, the latter being essential for active transport.

Key words: Intestinal calcium transport – Uremia – Parathyroid hormone – 1,25-DHCC

Intestinal calcium absorption is known to be impaired in human renal insufficiency [6, 10, 11, 16, 20, 27]. According to data on the time course of the fractional absorption of radiocalcium a main defect can be localized in the proximal small intestine, the distal absorption being less disturbed [5, 6, 10, 30]. These data are in agreement with the finding of a decreased calcium binding protein in the duodenal mucosa of patients suffering from renal disease [24]. The calcium binding protein is synthesized in response to the secretion of a renal metabolite of vitamin D₃, 1,25-Dihydroxycholecalciferol (1,25-DHCC) [12]; its serum concen-

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tration is low in renal failure [22]. Since in azotemia the distal intestinal calcium transport seems to behave differently in comparison to the proximal transport the calcium transport in vitro of a distal gut site in rats was studied under various experimental conditions. Effects of low calcium diet, azotemia, parathyroidectomy and 1,25-DHCC treatment were investigated singly and in combination.

Methods

Animal Preparation

Male albino rats of the Zz-cara strain (Central Biology Laboratory, University Hospital Zurich) were obtained as weanlings weighing 50–60 g. The 5/6-nephrectomy was accomplished by a modification of the method of McCance and Morrison [23]. An equal number of animals were sham-operated by exposing both kidneys with a time interval of seven days.

After operation 10 rats of the nephrectomized and 10 rats of the sham operated group were kept for two weeks on a diet with normal content of calcium (0.95%, Altromin 1000). The remaining rats of both groups were kept for the same time on a low calcium diet (0.05%, Altromin 1031). Both diets contained 0.80% of phosphorus and 500 I.U./kg of vitamin D₃. Sham operated animals received the amount of food eaten by the experimental rats during the previous day. All animals were allowed free access to demineralized water supplemented with 4.5 g of sodium chloride per liter to prevent effects of sodium loss in the nephrectomized groups [23].

After two weeks on their respective diet 10 animals of the nephrectomized and 10 animals of the sham-operated group both on low calcium diet were randomly selected and thyroparathyroidectomized under light ether anesthesia with the aid of a dissecting microscope. The criterion for successful removal of the parathyroid glands was a fall of the serum calcium concentration below 5.0 mg/100 ml 24 h postoperatively. 48 h after parathyroid surgery, intestinal calcium transport studies were performed.

In another experiment nephrectomized and control rats were kept for two weeks on the low calcium diet. Starting 5 days prior to sacrifice, 10 animals of the nephrectomized and the control group were injected i.p. daily with 40 pmoles of 1,25-DHCC (kindly donated by F. Hoffmann-La Roche, Basel). 48 h prior to sacrifice 5 rats of each group were thyroparathyroidectomized; the remaining 5 animals served as controls.

At the end of the experiment the animals were exsanguinated by abdominal aortic puncture.

Calcium Transport Studies

Gut segments measuring 5 cm in length were excised from the proximal duodenum and the distal ileum. They were everted and thoroughly washed with cold solution containing 0.146 M of NaCl and 0.004 M of KCl. After forming a sac, the inside (serosal surface) was filled with 0.5 ml of the following medium: NaCl 0.151 M, fructose 0.02 M, CaCl₂ 0.0008 M, Na₂HPO₄ 0.004 M (pH 7.4). The filled sac was placed in an Erlenmeyer's flask containing 5.0 ml of the same medium which was gassed with 100% O₂ before the experiment. The flasks were placed in an oscillating water bath at 37°C. After an incubation period of 2 h aliquots of the medium (inside and outside) were taken for calcium measurements. The active transport of calcium was expressed as the ratio of the total calcium concentration (mg/100 ml) in the serosal (inside) and the mucosal (outside) medium after incubation (s/m-ratio) [32].

Chemical Analysis

The total calcium was measured by automatic ethylene-glycol-bis (beta-aminoethyl-ether)-N,N'-tetraacetic acid (EGTA) titration using calcein as fluorescent indicator (Marius calcium titrator, Utrecht, The Netherlands, CV 1.7%). The inorganic phosphorus was measured without

deproteinisation of the samples by a color reaction using malachitgreen as reagent (Hoffmann-La Roche Diagnostica, CV 3%). The total protein was measured by means of a refractometer (American Optical, Buffalo, N.Y. CV 1.5%). Magnesium was determined by a color reaction employing alcoholic solution of xylic blue as indicator (E. Merck, Darmstadt, Germany, Merckotest Diagnostica, CV 2.5%). Urea determination was performed using urease as hydrolyzing enzyme and measuring colorimetrically the produced ammonia by the phenol-hydrochloride reaction of Berthelot (Boehringer, Mannheim, Germany, Diagnostica, CV 2.5%).

Statistical Analysis

Statistical evaluation was carried out using Student's *t*-test for unpaired data.

Results

Body Weight and Serum Chemistries (Table 1)

Body weights did not differ significantly between all groups of rats. Serum protein concentrations are similar in all groups of animals investigated. 5/6-nephrectomy produced a broad spectrum of high serum urea concentrations; mean values were similar for groups on normal and low calcium intake. The rats used for the additional experiments evaluating effects of parathyroidectomy and 1,25-DHCC-substitution showed lower urea concentrations than the other groups of 5/6-nephrectomized rats due to less radical nephrectomy. In sham-operated animals low calcium diet produced a significant decrease of the serum calcium concentration whereas the serum phosphorus was slightly decreased when compared with animals on a normal calcium diet. In 5/6-nephrectomized rats, low calcium diet resulted in a further decrease of the serum calcium as compared to sham-operated animals on the same diet while the serum phosphorus concentration was higher. 5/6-nephrectomized rats on normal calcium diet did not show hypocalcemia but slight hyperphosphatemia. The serum magnesium concentrations were similar for parathyroid intact rats on normal and low calcium diet.

In thyroparathyroidectomized rats lower serum levels of calcium and the higher level of phosphorus confirmed the successful ablation of the parathyroid glands. The serum calcium level was even more depressed when parathyroidectomy was combined with partial nephrectomy. The serum calcium concentration approached the normal range in nephrectomized rats given 1,25-DHCC whereas a lower level of phosphorus was observed. Nephrectomy plus thyroparathyroidectomy while supplemented with 1,25-DHCC resulted in an increase, but not in the normalisation of the serum calcium whereas the high inorganic phosphorus concentration showed a further increase. Serum magnesium concentrations were markedly elevated in rats on a low calcium diet supplemented with 1,25-DHCC.

Calcium Transport Studies

Duodenal and Ileal Site of Maximal Transport. The s/m ratios obtained from 5 partially nephrectomized rats on the low calcium diet are shown on Figure 1.

Table 1

Condition	n	Diet % Ca	Weight g	Protein mg/100 ml	Urea mg/100 ml	Calcium mg/100 ml	(Ca prior to tptx mg/100 ml)	Phosphorus mg/100 ml	Magnesium mg/100 ml
sham-op	5	0.95	96 ± 2	6.4 ± 0.3	33 ± 6	9.6 ± 0.4		8.4 ± 1.1	1.8 ± 0.2
nx	7	0.95	99 ± 5	6.1 ± 0.6	128 ± 27	8.9 ± 1.4		11.5 ± 3.5 ^e	2.6 ± 0.5
sham-op	5	0.05	95 ± 3	6.2 ± 0.3	34 ± 8 ^a	8.9 ± 0.2 ^b		7.0 ± 0.5	2.0 ± 0.1
nx	9	0.05	94 ± 4	6.0 ± 0.3	121 ± 57 ^a	5.6 ± 1.0 ⁱ		10.0 ± 1.6 ^e	1.9 ± 0.2
tptx	5	0.05	102 ± 8	6.6 ± 0.5	31 ± 23	4.2 ± 0.5 Å ^j	(8.7 ± 0.9)	11.9 ± 1.1 ^d	1.2 ± 0.1 ^f
nx + tptx	5	0.05	96 ± 5	6.1 ± 0.4	180 ± 46 ^a	3.5 ± 1.9 Å ^j	(5.7 ± 1.0)	12.5 ± 2.4	1.5 ± 0.1 ^f
nx + 1,25-DHCC	5	0.05	112 ± 8	6.1 ± 0.4	68 ± 5 ^b	7.9 ± 1.2 Å ^k		7.7 ± 1.3 ^e	3.2 ± 0.1 ^g
nx + tptx + 1,25-DHCC	5	0.05	109 ± 11	6.7 ± 0.1	63 ± 9 ^b	4.1 ± 0.4 Å ^j	(9.3 ± 1.2)	15.3 ± 4.7 ^d	2.6 ± 0.3 ^g

^a Different from sham-operated controls of the same group, $P < 0.05$; ^b different from corresponding groups without supplementation of 1,25-DHCC, $P < 0.05$; ^c different from sham-operated controls of the same group, $P < 0.05$; ^d different from corresponding groups with intact parathyroid glands, $P < 0.05$; ^e different from corresponding group without supplementation of 1,25-DHCC, $P < 0.05$; ^f different from corresponding groups with intact parathyroid glands, $P < 0.05$; ^g different from corresponding groups without supplementation of 1,25-DHCC, $P < 0.05$; ^h different from corresponding group on normal calcium diet, $P < 0.05$; ⁱ different from corresponding group on normal calcium diet, $P < 0.005$; ^j different from values prior to tptx, $P < 0.05$; ^k different from corresponding group without supplementation of 1,25-DHCC, $P < 0.05$; sham-op: sham-operated; nx: nephrectomized; tptx: thyroparathyroidectomized

Fig.1. Calcium transport by different segments of small intestine in azotemic rats on low calcium diet (0.05% calcium). All values are mean $\pm$ S.D.

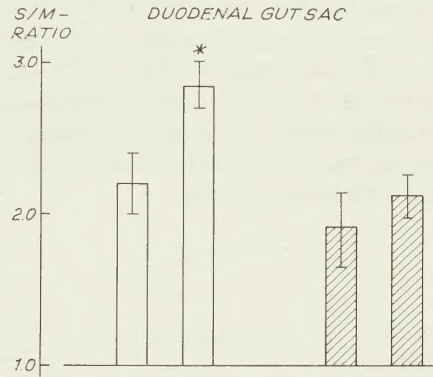
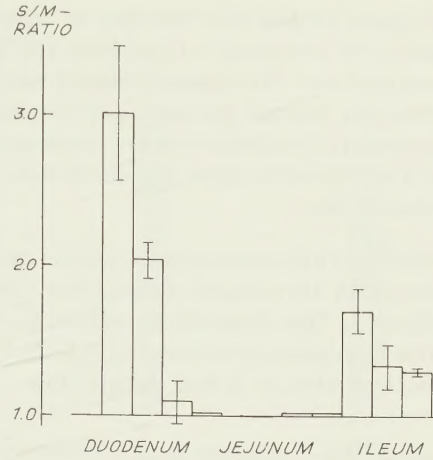
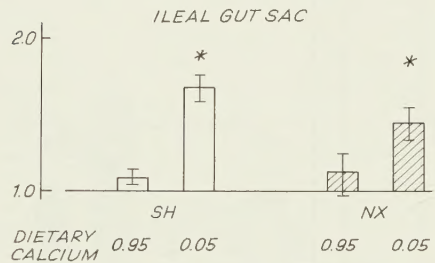


Fig.2. Intestinal calcium transport in 5/6-nephrectomized (batched bars) and sham-operated rats on normal and low calcium diet. Significant differences ($P < 0.05$) are indicated by asteriks at top of a column comparing corresponding segments on normal and low calcium diet. All values are mean $\pm$ S.D.



Only in the most proximal three segments of the duodenum and in the most distal three segments of the ileum s/m-ratios above 1.0 were found indicating calcium transport against concentration gradients. Gut sacs from all other sites of small intestine showed s/m-ratios of 1.0 indicating no active transport. Maximal s/m-ratios were found in the proximal 5 cm-segment of the duodenum and in the ileum in a 5 cm-segment beginning 15 cm proximal from the ileocecal valve. For further studies these two sites were investigated and referred to as duodenal and ileal gut segments.

Response to Low Calcium Diet in Intact and 5/6-Nephrectomized Rats. Figure 2 shows the s/m-ratios of duodenal and ileal everted gut sacs obtained from sham-operated and 5/6-nephrectomized rats on normal and low calcium diet. In the duodenal everted gut sacs only sham-operated animals increased the calcium transport in response to a low calcium diet. In the ileal segment sham-operated as well as nephrectomized rats showed an increased s/m-ratio when placed on a low calcium diet.

Effect of Thyroparathyroidectomy in Intact and 5/6-Nephrectomized Rats. The influence of thyroparathyroidectomy upon active calcium transport is shown in Figure 3. The duodenal as well as the ileal s/m-ratio were markedly depressed after thyroparathyroidectomy in both the nephrectomized (nx) and the sham (sh) operated rats on a low calcium diet.

1,25-DHCC Treatment in 5/6-Nephrectomized and 5/6-Nephrectomised and Parathyroidectomized Rats. Supplementation with 1,25-DHCC of nephrectomized and nephrectomized-thyroparathyroidectomized rats resulted in an increase of the duodenal s/m-ratios, whereas the ileal transport was augmented only in parathyroid-intact animals (Fig. 4). As mentioned above the animals used for this additional experiment showed significantly lower serum urea levels compared to all other groups of 5/6-nephrectomized rats. In spite of less severe uremia proximal and distal intestinal calcium transport was impaired to the same extent as seen in rats with severe uremia.

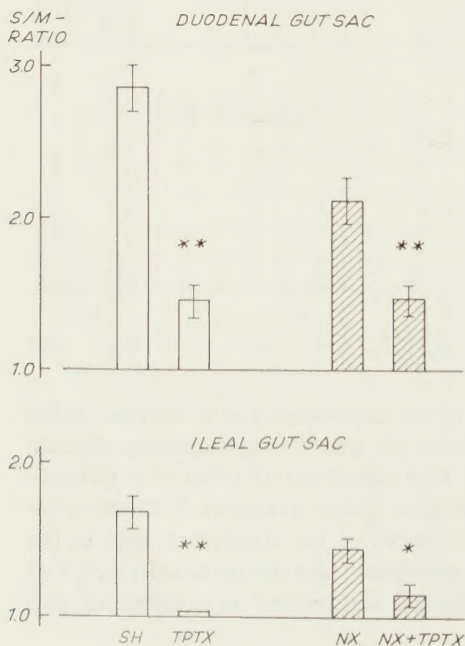


Fig. 3. Influence of thyroparathyroidectomy on active duodenal and ileal calcium transport on low calcium diet (0.05% calcium). Nephrectomized rats are indicated by hatched columns. Significant differences are indicated by asteriks at top of a column comparing corresponding segments in thyroparathyroidectomized and intact animals. ** $P < 0.01$, * $P < 0.05$. All values are mean $\pm$ S.D.

Fig. 4. Influence of physiologic dose of 1,25-DHCC (40 pmoles given intraperitoneally daily 5 days before sacrifice) on active duodenal and ileal calcium transport in 5/6-nephrectomized rats on low calcium diet (0.05% calcium). Significant differences are indicated by asteriks ($P < 0.05$) at top of a column comparing corresponding segments without and with supplementation of 1,25-DHCC and by crosses ($P < 0.05$) at top of a column comparing corresponding segments of thyroparathyroidectomized and intact animals with supplementation of 1,25-DHCC. Intestinal segments from animals, supplemented with 1,25-DHCC are indicated by shaded columns. Values of s/m ratio are mean $\pm$ S.D.

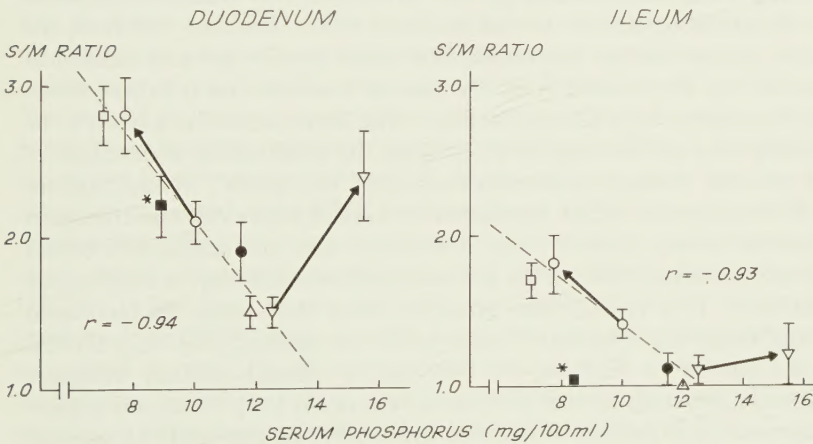
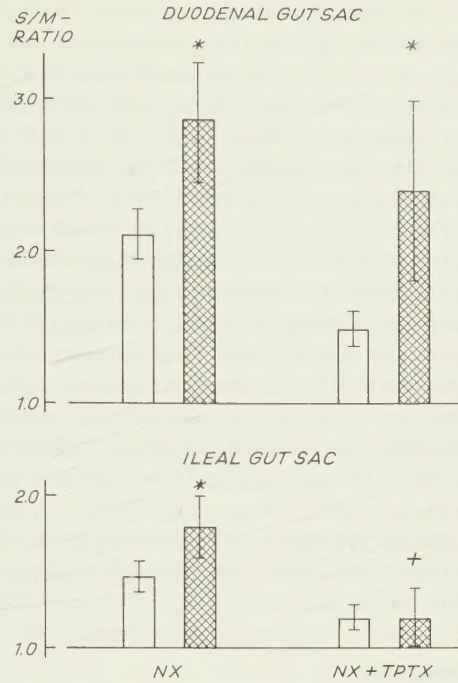


Fig. 5. Relationship between in vitro calcium transport (s/m-ratio) and serum phosphorus concentrations. Partially nephrectomized rats on normal (●) and low (○) calcium diet; sham-operated rats (■, □); sham-operated parathyroidectomized rats (Δ); partially nephrectomized plus parathyroidectomized animals (▽). →: supplementation with low dose 1,25-DHCC. *: Rats with intact kidney function on normal calcium diet not included in correlation. All values are mean $\pm$ S.D.

Serum Phosphorus-s/m Calcium Transport Relationship. Between mean serum phosphorus concentrations and s/m calcium ratios of duodenal as well as ileal gut sacs a close inverse correlation can be demonstrated. A deviation from this correlation is observed for partially nephrectomized and parathyroidectomized rats substituted with 1,25-DHCC and for sham-operated rats on the normal calcium diet, which show no transport by the ileal gut sac. During serum phosphorus concentrations of 7–8 mg/100 ml (intact and nephrectomized, 1,25-DHCC supplemented rats) a normal response of the calcium transport to a low calcium diet can be demonstrated. With serum phosphorus levels of 12–13 mg/ml however as seen in parathyroidectomized, kidney intact or partially nephrectomized rats, only a small duodenal and no ileal response of the calcium transport to a low calcium diet challenge can be recognized. Partial nephrectomy alone resulted in intermediate phosphorus concentrations and calcium transport indices. Very high serum phosphorus concentrations occurred in nephrectomized, parathyroidectomized rats given 1,25-DHCC; under these conditions an improvement of the gut calcium transport was demonstrable in the duodenum but was lacking in the ileum. 1,25-DHCC treatment in the absence of parathyroid hormone resulted in a new setting of the relationship between serum phosphorus concentration and s/m calcium transport ratio.

Discussion

The estimation of the transport of calcium across the intestinal wall was performed using the *in vitro* everted gut sac technique. This method determines the transfer of substances across the full thickness of the intestinal wall from the mucosal to the serosal surface. In functionally intact everted gut sacs calcium is absorbed rapidly by the mucosa from the outside medium and is subsequently more slowly transferred to the inside medium. The latter process is known to be the rate limiting step in the transfer of calcium. By establishing differences of serosal and mucosal calcium concentrations, the “end point” of the calcium transport was documented, which represents the sum of active calcium transport steps. It must be noted, however, that s/m-ratios may not adequately reflect calcium transport characteristics of the gut sacs, particularly if there is a difference in water transport. It is evident that processes other than active or facilitated calcium transport are not adequately explored by the method [26]. 1,25-DHCC treatment was shown to increase the mucosal to serosal calcium transport without markedly affecting serosal to mucosal transport [31]. Since our experiments concentrate on situations of variable availability of 1,25-DHCC, we suggest to investigate by means of the everted gut sac technique effects on calcium transport which are real.

On a normal calcium diet, calcium transport as observed by the *in vitro* gut sac method was demonstrable in the duodenum but not in the ileum of sham-operated non uremic rats. These data are in accord with previous studies demonstrating active calcium transport to occur only in the first 20 cm of the duodenum [18]. *In vivo* studies using a bolus of calcium-47 showed calcium absorption to occur in the duodenum [21].

Azotemia is known to impair duodenal calcium transport *in vitro* [2, 14, 17, 31] and *in vivo* [6, 11]. In our study 5/6-nephrectomized rats did not exhibit significantly different calcium transport when compared to control animals. The reason might be that pair feeding causes some degree of malnutrition in control animals; under such conditions active calcium transport in the duodenum has been shown to be impaired [1, 17]. By the *in vitro* technique using everted gut sacs the decrease of s/m-ratios of azotemic animals in the duodenum has been found to be about 50 percent, depending somewhat on the concentration of calcium in the bathing medium [2, 14, 17, 31]. On a normal calcium diet the ileal s/m-ratios of both sham-operated and 5/6-nephrectomized rats were close to 1.0 indicating no active transport to be demonstrable. In sham-operated animals the low calcium diet resulted in an increase of the duodenal s/m-ratio of 34 percent compared with sham-operated controls on a normal calcium diet. The ileal s/m-ratio was 1.6, indicating active transport to be demonstrable during low calcium diet. In 5/6-nephrectomized rats no increase of duodenal s/m-ratios were found; in the ileum, however, an increase of the s/m-ratio of 50 percent of that found in intact animals was demonstrated.

To our knowledge the active calcium transport of ileal gut segments has not been studied in uremic animals. Findings of fractional intestinal calcium absorption not being different in uremic and control rats [5] are compatible with the view that distal gut segments might compensate for impaired proximal calcium transport.

The increase of the active calcium transport induced by a low calcium diet was found to depend on the parathyroid hormone concentration and on the 1,25-DHCC-synthesis [13]. Low calcium diet stimulates parathyroid hormone secretion in uremic rats [14]. Parathyroid hormone mobilizes calcium from the bone [3], increases tubular reabsorption of calcium in the kidney [15] and increases production of 1,25-DHCC from circulating 25-hydroxycholecalciferol [19, 25]. The lack of increase of the duodenal calcium transport during low calcium diet in partially nephrectomized rats suggests impaired 1,25-DHCC-synthesis in spite of secondary hyperparathyroidism [24]. In the kidney parathyroid hormone brings about an increased cyclic AMP production and a reduced tubular reabsorption of phosphorus. The low inorganic phosphorus level of the cell increases the activity of the 1-alpha-hydroxylase enzyme system responsible for the production of 1,25-DHCC. It has been shown that rats maintained on a diet low in phosphorus produce 1,25-DHCC from 25-OHCC whether they have been thyroparathyroidectomized or not [28]. In nephrectomized rats with a high level of inorganic phosphorus in the serum it can be assumed that the high phosphorus concentration inhibits parathyroid hormone to stimulate 1,25-DHCC synthesis. By this inhibition, the diminished 1,25-DHCC synthesis due to loss of functioning renal tissue is further accentuated.

The simultaneous increase of the ileal calcium transport raises the question whether the distal gut sac calcium transport is less dependent on the 1,25-DHCC mediated transport mechanisms. Since 5/6-nephrectomized rats on a low calcium diet have been shown to have excessively elevated parathyroid hormone levels in the blood [14], one can speculate, that parathyroid hormone could influence ileal active calcium transport directly by non 1,25-DHCC mediated effects. Beside of

the 1,25-DHCC dependent calcium transport an independent change was demonstrated in the ileum of vitamin D depleted rats [4] as well as in primary hyperparathyroidism [7]. Calcium transport correlated with water transport during vitamin D deficiency [4]. Activation of a calcium dependent phosphatase [8] might reflect another mechanism by which parathyroid hormone influences the calcium transport. Acute thyroparathyroidectomy performed after an adaptation period to the low calcium diet diminishes the s/m-ratio in the duodenum of uremic and control rats to very low values. The ileal calcium transport decreased more in intact than in uremic animals. This might point towards some role of very high as compared to high parathyroid hormone levels in uremic and control rats respectively [14]. It also indicates that the calcium transport at least at the ileal site is still modulated inspite of severe hypocalcemia and hyperphosphatemia and inspite of 1,25-DHCC deficiency.

In agreement with others [9] the supplementation with 1,25-DHCC of uremic parathyroid intact rats shows that very small doses are capable of stimulating active calcium transport. Inspite of uremia duodenal and ileal s/m-ratios were not different from those of sham-operated animals on a low calcium diet indicating that 1,25-DHCC supplementation brings about adaptive changes to low calcium diet not different from those seen in intact animals. This suggests that uremia per se does not alter the adaptive mechanism of the intestine.

Equal doses of 1,25-DHCC induced a similar percent increase of the duodenal calcium transport also in uremic parathyroidectomized rats. The ileal calcium transport, however, remained unchanged. This finding supports the view that a 1,25-DHCC independent regulation is of importance in the distal small intestine. The positive response to 1,25-DHCC of the ileum in parathyroid intact but not in parathyroidectomized uremic rats suggests that parathyroid hormone and 1,25-DHCC might act in concert to promote calcium transport in the distal gut.

The close relationship between the serum phosphorus concentration and s/m calcium ratios points towards the importance of phosphorus for the intestinal calcium transport. From data in uremic parathyroidectomized, 1,25-DHCC supplemented rats it can be suggested that parathyroid hormone in concert with 1,25-DHCC is involved in the phosphorus- s/m ratio correlation; 1,25-DHCC replacement in the absence of parathyroid hormone only partially restores duodenal calcium transport, but also results in extremely high serum phosphorus concentrations.

A decreased activity of the 1- α -hydroxylase was demonstrated in the rat after partial nephrectomy or ureteral ligation suggesting loss of renal parenchyma and high phosphorus levels to be involved [29]. According to the data presented in this paper the serum phosphorus concentration in concert with the 1,25-DHCC and the parathyroid hormone status seem to be closely linked to the intestinal calcium transport. Furthermore, parathyroid hormone related effects on the distal intestinal calcium transport seem to be activated under certain conditions.

The contribution of different factors involved in net ileal mucosal to serosal calcium transport and its modulation in uremia remains to be further elucidated in order to fully understand the alteration of proximal and distal intestinal calcium transport in uremia.

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